REMARKS

Reconsideration and withdrawal of the rejections of the claimed invention is respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

With the entry of the present amendment, claims 1, 9, 11, 13 and 14 are now pending in this application. No new matter has been added by this amendment and the nature of the claim amendments would not justify a final rejection if new references were applied in the next communication as the (S)-(-)-amlodipine gentisate compound was explicitly disclosed in the specification, see e.g. Examples 2 and 3.[1]

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

III. THE 35 U.S.C. 112, 1st PARAGRAPH REJECTION HAS BEEN OVERCOME

Claims 1-12 were rejected as allegedly being non-enabling for the full scope of the invention written. While the applicants do not agree with the rejection, in order to advance prosecution, the applicants request reconsideration of this rejection in light of the amendments made to the claims which restrict the claims to the treatments which were acknowledged as being enabled. Applicants reserved the right to pursue the scope of the original subject matter in a continuation application.

VII. THE 35 U.S.C. 103(a) REJECTION HAS BEEN OVERCOME

Claims 1-12 were rejected as allegedly being obvious by Campbell et al. (EP 0089167 - "Campbell"). The applicants request reconsideration of this rejection for the following reasons in light of the amendments made to the claims which restrict the claims to describe a specific stereoisomer of an amlopidine salt, i.e. (S)-(-)-amlodipine gentisate.

All limitations not taught

The Office Action refers to page 2, lines 47-51 (intended to be 19-25?) as not excluding gentisate salt. However, the initial burden for establishing *prima facie* obviousness resides with the Office and that burden includes the requirement that all limitations be taught or suggested by the prior art. With regard to gentisate salts, there is no evidence of record to suggest that gentisate salts are taught or suggested by Campbell, i.e. the gentisate (an o-carboxyl- p-dihydroxyphenyl group) is not represented in the passage cited in Campbell.

Furthermore, the applicants' compounds claimed are not only a gentisate salt, but a specific stereoisomer of the gentisate salt form of amlodipine which Campbell also does not teach or suggest.

Evidence of secondary considerations

Part of the *Graham* requirements for making evaluations of obviousness includes reviewing evidence of secondary considerations.

In the present invention, the applicants have compared the effects of (S)-(-)-amlodipine gentisate against (±) amlodipine besylate.[2] Besylate is a phenyl sulfate and is encompassed by Campbell ("...non-toxic acid addition salts containing pharmaceutically acceptable anions, such as...sulphate..." – see page 2, lines 21-23).

As stated in MPEP 716.02(a) – "'Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness.' No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)". In the present application, the applicants have shown not just one, but three unexpectedly superior properties over the prior art.

Experimental example 2 provided a stability comparison of (S)-(-)-amlodipine gentisate vs. (±) amlodipine besylate and (S)-(-)-amlodipine besylate. In Tables 2 and 3 (temperature and humidity test), at all the tested times during the eight week testing period, (S)-(-)-amlodipine gentisate had superior stability as evidenced by its content. Table 4 (light stability) also showed superior stability as evidence by its content.

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[1] MPEP 904.03 states in part "[i]t is normally not enough that references be selected to meet only the terms of the claims alone, especially if only broad claims are presented; but the search should, insofar as possible, also cover all subject matter which the examiner reasonably anticipates might be incorporated into applicant's amendment."

[2] (±) amlodipine besylate is also known as the active ingredient of Norvasc®. The seller, Pfizer, Inc., is the assignee of the Campbell reference.

Experimental example 3 provided a test of active ingredients in the blood after oral administrations for (S)-(-)-amlodipine gentisate vs. (±) amlodipine besylate. As noted in the description after Table 5, "...S-(-)-amlodipine gentisate showed the highest concentration [as compared to (±) amlodipine besylate] in blood after administration in rats during the physiologically useful period of 4-6 hr after the administration..." Even at the end of the 8-week testing period, there was still a 32.5% increase in concentration ([(0.220 – 0.166)/0.166] x 100%) for (S)-(-)-amlodipine gentisate vs. (±) amlodipine besylate.

Experimental example 4 provided a test of anti-hypertensive effects of (S)-(-)-amlodipine gentisate vs. (±) amlodipine besylate. From Tables 6 and 7, it can be seen that using half the dosage, i.e. 1.25 mg/kg which represents a 50% decrease in dosage, for (S)-(-)-amlodipine resulted in a loss of only 4.8% for the decrease in blood pressure ([(20.8 – 19.8)/20.8] x 100%) for a 2.5 mg/kg dosage of (±) amlodipine besylate. Furthermore, when the same 2.5 mg/kg dosage is used for (S)-(-)-amlodipine, the claimed compounds exhibits a 17.7% ([(24.5 – 20.8)/20.8] x 100%) more of a decrease in blood pressure.

As such, the applicants have shown evidence of superior results with regard to stability, blood level concentrations and anti-hypertensive effects and the Campbell reference does not teach or suggest any of these unexpected effects.

Conclusion

For either of the above reasons, the applicants' invention as claimed is not obvious over the Campbell reference.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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